## REMARKS

Upon entry of the amendment claims 59, 66, 78, 84, 86, 87, 89 and 91-92 will be pending in the application. Claims 59 and 78 have been amended. Support for the amendments to claims 59 and 78 appears in the specification at, e.g., paragraph 8, Support for new claims 91-92 appears in, e.g., paragraph 4 of the specification. No new matter is added.

Rejections under 35 § USC 103(a)

Claims 59, 66, 78, 84, 86-87 and 89 are rejected as unpatentable over Shapiro et al., Diabetologia 45:224-230, 2002 ("Shapiro") in view of Nardi, US Patent No. 5,885,956 ("Nardi"). The rejection is traversed.

A *prima facie* case of obviousness requires that "either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *See* MPEP 706.02(j) citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Knowledge of the disclosure provided by the instant application must be put aside when determining whether the claimed invention would have been obvious. *See* MPEP 2142.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one ordinary skill in the art. *See* MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385, 1396 (2007). Furthermore, a statement that modifications of the prior art to meet

the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See* MPEP §2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (emphasis original).

The rejected claims are drawn to a pharmaceutical composition comprising an agent for suppressing an immune response and a gastrin/CCK receptor ligand wherein the agent is a rapamycin and the gastrin is gastrin17(Leu15) and a EGF receptor ligand is absent, (claim 59 and its dependent claims), or to a method of treating a diabetic subject comprising administering to said subject an agent that increases islet neogenesis and an agent that suppresses an immune response, wherein said agent that increases islet neogenesis is gastrin17(Leu15) and a EGF receptor ligand is absent, and the agent that suppresses an immune response is a rapamycin (claim 78 and its dependent claims). New claims 91 and 92 require that the recited pharmaceutical composition include rapamycin and a composition for islet neogenesis that consists of gastrin17(Leu15).

No modification of Shapiro or Nardi would have rendered the claimed invention prima facie obvious. The Examiner alleges Nardi contemplates "using a composition comprising gastrin/CCK receptor ligand for treating diabetes mellitus (claims 1-4, 6-8)." Applicants disagree with this characterization of Nardi. Nardi teaches the use of a combination of gastrin and EGF and teaches that it is the combination of EGF and gastrin that is effective. Notably, claims 1-4 and 6-8 of Nardi all refer to administering to an individual a "composition comprising a proteinaceous gastrin/CCK receptor ligand and a proteinaceous EGF receptor ligand." (Nardi,

claim 1). But there is no teaching or suggestion in Nardi that gastrin17(Leu15) alone is effective.

Further, Nardi specifically teaches away from the use of gastrin in the absence of EGF. Example 2 of Nardi teaches that "sustained expression of gastrin in the postnatal pancreas alone does not stimulate islet cell growth." (*See*, Nardi at column 10, lines 22-24). Thus, one of skill in the art would not be motivated to use gastrin 17(Leu15) in the absence of an EGF receptor ligand as a treatment for diabetes mellitus because Nardi indicates that gastrin without an EGF receptor ligand would not work in a postnatal pancreas and therefore the claimed invention cannot be said to be predictable in view of Nardi. Additionally, since Nardi indicates that gastrin in the absence of EGF would not work in a postnatal pancreas, one of skill in the art would have no expectation of success in using gastrin in the absence of an EGF receptor.

Shapiro does not cure the deficiencies of Nardi. Shapiro merely deals with the effects of the combination of two immunosuppressive agents and provides no information that would point one of skill in the art to gastrin17(leu15) as required by the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness.

Applicants petition for a two month extension of time for responding to the Office action (petition enclosed). Please credit any overpayment or charge any deficiencies to Deposit Account No. 50-0311, Reference No. 24492-010NATL.

Respectfully submitted,

David H. Johnson, Reg. No. 41,874
Attorney for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
**Customer Number 30623**

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